

**IN THE SPECIFICATION:**

Please amend the specification as follows:

Please delete the paragraphs on page 9, line 21 to page 10, line 28 and replace them with the following paragraphs:

Figure 1. Structure-based sequence alignment of a selected number of bromodomains (SEQ ID NOS 7-42). The sequences were aligned based on the NMR-derived structure of the P/CAF bromodomain, and the predicated four  $\alpha$ -helices are shown in green boxes. Bromodomains are grouped on the basis of the sequence and/or functional similarities as described by Jeanmougin *et al.*, [Trends in Biochemical Sciences, 22:151-153 (1997)]. Residue numbers of the P/CAF bromodomain are indicated above its sequence. Three absolutely conserved residues, corresponding to Pro751, Pro767, and Asn803 in the P/CAF bromodomain, are shown in red. Highly conserved residues are colored in blue. The residues of the P/CAF bromodomain that interact with acetyl-histamine, as determined by intermolecular NOEs, are indicated by asterisks. The ZA loop, which is critical for acetyl-lysine binding, for each of the indicated bromodomains is also identified. The underlined residues were changed individually by site-directed mutagenesis to Ala. Genbank accession numbers for the proteins are as indicated in Table 8, in the Example below, along with the SEQ ID NOS. for the bromodomain sequences.

Figures 2A-2H depict the structure of the P/CAF bromodomain. Figures 2A-2B shows the stereoview of the  $C_\alpha$  trace of 30 superimposed NMR-derived structures of the bromodomain (residues 722-830). The N-terminal four residues (SKEP) (residues 1-4 of SEQ ID NO: 7) which are structurally disordered are omitted for clarity. For the final 30 structures, the root-mean-square deviations (RMSDs) of the backbone and all heavy atoms are  $0.63 \pm 0.11\text{\AA}$  and  $1.15 \pm 0.12\text{\AA}$  for residues 723-830, respectively. The RMSDs of the backbone and all heavy atoms for the four  $\alpha$ -helices (residues 727-743, 770-776, 785-802, and 807-827), are  $0.34 \pm 0.04\text{\AA}$  and  $0.87 \pm 0.06\text{\AA}$ , respectively. Figures 2C-2D show the stereoview of the bromodomain structures from the bottom of the protein, which is rotated approximately  $90^\circ$  from the orientation in Figures 2A-2B. Figure 2E shows the Ribbons [Carson, M., *J. Appl. Crystallogr.* 24:958-961 (1991)] depiction of the averaged minimized NMR structure of the P/CAF bromodomain. The orientation of Figure 2E is as shown in Figures 2A-2B. Figures 2F-2G are schematic representations of the overall topology of the up-and-down four-helix bundle folds

with the opposite handedness. The left-handed fold is seen in bromodomain, cytochrome  $b_5$ , and T4 lysozyme (left, Figure 2F), whereas the right-handed four-helix bundles are observed in proteins such as hemerythrin and cytochrome  $b_{562}$  (right, Figure 2G) [Richardson, J., *Adv. Protein Chem.*, **34**:167-339 (1989); Presnell and Cohen, *Proc. Natl. Acad. Sci. USA* **86**:6592-6596 (1989)]. Figure 2H is a molecular surface representation of the electrostatic potential (blue = positive; red = negative) of the bromodomain calculated in GRASP [Nicholls *et al.*, *Biophys. J.* **64**:166-170 (1993)]. The hydrophobic and aromatic residues (Tyr809, Tyr802, Tyr760, Ala757, and Val752) located between the ZA and BC loops are indicated.

Please delete the paragraph on page 25, lines 8-13 and replace it with the following paragraph:

All of the peptides/fragments of the present invention can be modified by being placed in a fusion or chimeric peptide or protein, or labeled *e.g.*, to have an N-terminal FLAG-tag, or H6 tag (SEQ ID NO: 45). In a particular embodiment the P/CAF bromodomain fragment can be modified to contain a marker protein such as green fluorescent protein as described in U.S. Patent No. 5,625,048 filed April 29, 1997 and WO 97/26333, published July 24, 1997 each of which are hereby incorporated by reference herein in their entireties.

Please delete the paragraph on page 56, line 29 to page 57, line 18 and replace it with the following paragraph:

The modular bromodomain structure supports the idea that bromodomain can act as a functional unit for protein-protein interactions. The observation that bromodomains are found in nearly all known nuclear HATs (A-type) that are known to promote transcription-related acetylation of histones on specific lysine residues, but not present in cytoplasmic HATs (B-type), prompted the determination of whether bromodomains can interact with acetyl-lysine (AcK). The NMR titration of the P/CAF bromodomain were performed with a peptide (SGRGKGG-AcK-GLGK) (SEQ ID NO: 46) derived from histone H4, in which Lys8 is acetylated (Lys8 is the major acetylation site in H4 for GCN5, a yeast homologue of P/CAF). Remarkably, the bromodomain could indeed bind the AcK peptide. Moreover, this interaction appeared to be specific, based on the  $^{15}\text{N}$ -HSQC spectra which showed that only a limited number of residues underwent chemical shift changes as a function of peptide concentration (Figure 3A). Conversely, the NMR titration

of the bromodomain with a non-acetylated, but otherwise identical H4 peptide, showed no noticeable chemical shift changes, demonstrating that the interaction between the bromodomain and the lysine-acetylated H4 peptide was dependent upon acetylation of lysine. The dissociation constant ( $K_D$ ) for the AcK peptide was estimated to be  $346 \pm 54 \mu\text{M}$ . This binding is likely reinforced through additional interactions between bromodomain-containing proteins and target proteins. Notably, many chromatin-associated proteins contain two or multiple bromodomains (Figure 1). Indeed, binding with another lysine-acetylated peptide (RKSTGG-AcK-APRKQ) (SEQ ID NO: 47) derived from the major acetylation site on histone H3 (residues 9-20) was also observed. Together, these data demonstrate that the P/CAF bromodomain has the ability to bind AcK peptides in an acetylation dependent manner.